Recurrence Phenomena After Immunoglobulin Therapy for Snake Envenomations: Part 2. Guidelines for Clinical Management With Crotaline Fab Antivenom

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Recurrent local and coagulopathic effects (worsening after clinical improvement) have been described after treatment with Fab antivenom for envenomation by North American crotaline snakes. Although similar phenomena have been described previously in snakebite, few studies have examined recurrence or its management. Recurrence is consistent with known venom and antivenom kinetics and dynamics. The clinical significance of late coagulopathy after snakebite is uncertain, but clinically significant bleeding is a possibility. Prevention and treatment of recurrence with Fab antivenom require repeated dosing for at least 18 hours, with close monitoring of at-risk patients in the follow-up period. Duration of therapy depends on individual risk factors and coagulation response.

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INTRODUCTION

Envenomation by crotaline (formerly crotalid) snakes such as rattlesnakes commonly produces local tissue injury and coagulopathy.[1-3] Although early treatment with antivenom can arrest or reverse these effects, local and coagulopathic recurrence have been described, raising concerns about a pharmacodynamic and pharmacokinetic mismatch between antivenom and venom components.[4-6] This phenomenon has not been directly addressed in the medical literature, before clinical studies of Fab antivenom.[5]

RECURRENCE PHENOMENA AFTER ANTIVENOM ADMINISTRATION

Local recurrence has been defined as renewed progression of edema, after the observer has determined that swelling has been arrested by initial antivenom treatment.[7] In the first trials, patients received initial doses of up to 8 vials of Crotalidae polyvalent immune Fab (ovine; CroFab, manufactured by Protherics; FabAV). Local recurrence was observed in 3 (27%) of 11 patients.[7] In the second phase of the FabAV clinical trials, patients received up to 12 vials for initial control and were then randomly assigned to either a scheduled dose (2 vials at 6, 12, and 18 hours after initial control) or an as-needed dosing group (2 vials as needed). Half of all patients in the as-needed dosing group and no patients in the scheduled group developed local recurrence ($P<.005$) 3 to 24 hours after initial treatment. All episodes of local recurrence responded to retreatment, although some patients had a second episode of local recurrence. There were no local recurrences beyond 24 hours.[8]

Coagulopathic recurrence involves an abnormality of platelet count, fibrinogen, prothrombin time (PT), or partial thromboplastin time (PPT) that became normal after treatment and subsequently became abnormal again. This phenomenon occurred over a different time course from that of local recurrence. Among the 38 FabAV recipients for whom data were complete, coagulopathy was documented in 28 (74%) before or within the first hour of treatment. Of the 38, 14 (37%) developed thrombocytopenia, 22 (58%) developed hypofibrinogenemia, and 17 (45%) developed prolonged PT or activated PTT (aPTT). Twenty (53%) cases were multicomponent. Coagulopathic abnormalities resolved in all patients; however, coagulopathy recurred in 20 (53%) patients (69% of the 28 patients with initial coagulopathy), 2 to 14 days after envenomation. The nature and degree of recurrent coagulopathy were consistent: significant recurrent thrombocytopenia ($<100,000/mm^3$) was noted at follow-up only in patients with prior significant thrombocytopenia (positive predictive value [PPV] 88%, negative predictive value [NPV] 100%, $P<.01$), and recurrent hypofibrinogenemia and PT/aPTT prolongation were noted at follow-up only in patients with early hypofibrinogenemia (PPV 59%, NPV 76%, $P<.05$) or prior fibrin degradation product (FDP) elevation (PPV 65%, NPV 89%, $P<.05$). In most cases, coagulopathy resolved spontaneously by 2 weeks.[9] Two patients received supplemental doses of FabAV during follow-up, 1 of whom showed a partial response of thrombocytopenia to additional antivenom at 6 and 9 days after envenomation.[4]

Recurrence of local signs of snake envenomation had not been reported as a distinct observation before the FabAV trials.[8] Others have described late or recurrent coagulopathy, however, after snakebite and treatment with Fab, Fab_2, and IgG products.[6,9-15] The infrequency of these reports, and the lack of extended laboratory monitoring of envenomated patients in general, make it difficult to estimate the true incidence and extent of the phenomenon.

In a study of 28 Malayan pit viper (*Calloselasma rhodostoma*) envenomations, 3 of 7 patients treated with horse IgG, 2 of 7 treated with horse Fab_2, and 3 of 9 treated with goat IgG had recurrent coagulopathy after initial response to treatment. Venom concentrations decreased to undetectable levels within 5 minutes of antivenom administration, but recurred at a median of 5 hours. Coagulopathic recurrence occurred later, at a median of 44 hours after the initial dose of antivenom.[16] In a separate study, an inverse relationship between the increase and decrease of venom and antivenom (horse IgG) titers was seen in a *C rhodostoma* bite, leading investigators to postulate that a depot of unneutralized venom is absorbed from the bite site for several days.[13] Similar rebounds of venom antigenemia have been reported in envenomation by *Echis pyramidum-complex*,[11] *Echis ocellatus*,[6] *Bungarus caeruleus*, and *Naja naja naja*.[14] In a study of 30 patients envenomated by *Vipera berus* and treated with horse Fab_2, severe recurrence of symptoms was reported in 2 patients. Additional antivenom was given with minimal effects in 1 patient and normalization of coagulation abnormalities 30 hours after the bite in a second patient.[15]

PATHOPHYSIOLOGY OF RECURRENCE

There are at least 4 possible explanations for the recurrence of local or coagulopathic effects of envenomation. These include (1) pharmacokinetic and pharmacodynamic mismatch between venom and antivenom, (2) separation of the circulating venom/antivenom complex after initial effective binding, (3) late onset of effect of venom components different from those initially active, and (4) development of host anti-antivenom immune response. These have been discussed in detail elsewhere.[5,8,17]

We believe that recurrence can best be understood in the context of crotaline venom and antivenom kinetics and dynamics. The half-life of FabAV is clearly less than that of venom in the body. After intravenous administra-

tion, FabAV binds immediately to venom components in the central circulation and probably at the site of local injury. There may be some penetration of antivenom at the bite site, but it is insufficient to neutralize all of the venom at that site. FabAV that does not immediately find and bind venom components (ie, unbound Fab) is cleared with an elimination half-life of 15 to 20 hours. Unneutralized venom at the bite site continues to present itself at the margin of local tissue injury, and to be absorbed into the central circulation such that eventually there is an insufficient concentration of antivenom in the circulation to neutralize it.[8,12]

The incidence of local recurrence is difficult to estimate,[7] but it occurs in a significant number of patients. Progression of local signs can continue for the first 24 to 36 hours in untreated cases, as well as in those treated with whole IgG antivenom.[18,19] Local recurrence appears to occur when the circulating concentration of FabAV falls rapidly during the distributive phase (distribution half-life approximately 2.5 hours), suggesting that there may be a critical antivenom concentration above which progression of local injury into adjacent tissue is arrested. Scheduled dosing during the first 24 hours appears to prevent local recurrence.[8]

Coagulopathies, on the other hand, may persist a few days to 2 weeks or more, associated with persistent or recurrent circulating venom components. This protracted course, relative to that of local injury, may indicate differences in clearance of various venom components from the bite site and the body. Recurrence appears to occur when the plasma concentrations of unbound Fab decrease below some critical value relative to the amount of venom remaining, suggesting that recurrence might be prevented by maintenance of plasma Fab levels. Unfortunately, the limited data available on retreatment allow few conclusions regarding the late use of antivenom once coagulopathy has recurred.

RATIONALE FOR LATE TREATMENT: RISK OF HEMORRHAGE

The clinical significance of coagulopathy many days after pit viper envenomation is uncertain. Coagulopathy in the first days after crotaline snakebite has been associated with life-threatening bleeding disorders,[20] and substantial ecchymosis is commonly described. Spontaneous bleeding, most commonly gingival, was noted at presentation in 11 (24%) of 46 patients bitten by *C rhodostoma*.[12] Hypofibrinogenemia alone is generally not associated with clinically severe bleeding,[21-23] even in the setting of fasciotomy.[24] No patient in the FabAV clinical trials experienced significant spontaneous bleeding, but 1 patient with hypofibrinogenemia developed minor bleeding after hemorrhoidectomy 12 days after envenomation.[5] Neither of 2 patients with *V berus* envenomation treated with Fab_2 antivenom who developed severe late coagulopathy (1 with no detectable fibrinogen and 1 with a platelet count of 14,000/mm^3), had bleeding complications.[15]

Although not directly related, other causes of thrombocytopenia, hypofibrinogenemia, and chemical coagulopathy offer some perspective on the risks associated with coagulation disorders.

In a study of 92 patients with acute leukemia, an increased incidence and severity of hemorrhage was observed with decreasing platelet counts below 50,000/mm^2, with a constant threat of serious bleeding below 10,000/mm^2, but no "threshold" count for intervention was established. The authors concluded that, in leukemia, thrombocytopenia alone was rarely responsible for hemorrhage.[25] Among 301 patients with significant thrombocytopenia while receiving myelosuppressive therapy for solid tumors, there were a total of 44 episodes of serious bleeding (1 per 115 patient-days when the platelet count was below 50,000/mm^2). The majority of these occurred in association with infection, additional coagulation abnormalities, or both.[26]

Since 1920, approximately 150 individuals have been identified with familial afibrinogenemia, an autosomal recessive disorder in which fibrinogen levels remain near-zero throughout life. Among the 150 recognized individuals have been 6 cases of splenic rupture, 2 traumatic and 4 spontaneous. Otherwise, the incidence of spontaneous hemorrhage in these patients is relatively low, with many patients surviving to adulthood before coagulopathy is recognized.[27] An additional 30 families have been identified with hypofibrinogenemia, which may represent a heterozygous form of the disorder. These patients are at increased risk of hemorrhagic complications from intercurrent surgery or significant trauma.[28] Spontaneous bleeding does not occur in hypofibrinogenemia unless fibrinogen levels decrease below 50 mg/dL.[29]

A retrospective review of 551 patients taking oral anticoagulants found that 12 of 323 men and 9 of 228 women experienced a major bleeding episode after a median of 30 months of anticoagulant treatment. No deaths occurred.[30] In 565 patients starting outpatient therapy with warfarin, major bleeding occurred in 65, was fatal in 10, and had a cumulative incidence of 3%, 11%, and 22% at 1, 12, and 48 months. Six clinical risk factors for major bleeding (relative risk >2) were identified: (1) age 65 years or older, (2) history of stroke, (3) history of gastro-

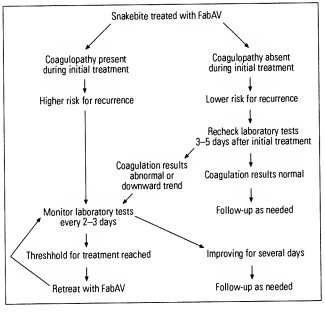
intestinal bleeding, (4) serious comorbid conditions, (5) atrial fibrillation, and (6) systolic blood pressure greater than 160 mm Hg. With increasing PT ratio (international normalized ratio [INR]), the incidence of bleeding increased. Relative risk became greater than 2 when INR was greater than 1.5.[31] A review of the hemorrhagic complications of anticoagulation therapy in 7 clinical trials found that the risk of bleeding was greater with INR >3.0. The risk of bleeding was associated with concomitant hypertension, cerebrovascular disease, serious heart disease, or renal insufficiency. Only 1 death was reported among 1,283 total patients in the 7 trials.[32]

Among 22 patients who developed significant thrombocytopenia during heparin therapy, 17 had serious thrombohemorrhagic complications.[33] Of 3,171 ESSENCE patients who took anticoagulants and had aPTT of 55 to 85 seconds, 209 experienced a major bleeding episode within 30 days, the majority occurring during coronary artery bypass grafting. "Very few" events occurred spontaneously.[34]

RECOMMENDATIONS

The indications for initial antivenom treatment of crotaline envenomation have been reviewed elsewhere.[18,35]

Figure.
Monitoring for coagulopathy in patients treated with Crotalidae Polyvalent Immune Fab (Ovine).



These include progressive local injury, particularly within the first 12 hours, and coagulopathy at any time after the snakebite. FabAV, at starting doses of 4 to 6 vials, may be used for all previously established criteria. In the past, however, the fear of anaphylaxis or serum sickness has often resulted in the decision to postpone or avoid administration of whole-IgG antivenom (Antivenin [Crotalidae] Polyvalent, Wyeth-Ayerst), especially for minimal envenomation. These risks appear substantially lower with FabAV, bringing the risk/benefit ratio in favor of more aggressive treatment of isolated local injury and mild early coagulopathies. Earlier treatment of minimal envenomation may prevent the more severe effects that often develop during observation.

Although control of ongoing local injury occurred promptly with initial FabAV treatment, approximately half of observed patients have had at least 1 episode of recurrence during the first 24 hours unless FabAV was given repeatedly. Scheduled doses of 2 vials of antivenom at 6, 12, and 18 hours appear to prevent local recurrence. Scheduled dosing does not eliminate the need to observe patients carefully for extension of local effects, however, because some may require additional antivenom during or after this time. These recommendations are based on relatively small numbers of patients and these conclusions may change as experience accumulates.

Patients who develop coagulopathy during the first 12 hours after FabAV treatment of envenomation have an approximately two-thirds chance of later recurrence. In theory, the potential for late coagulopathy may be masked in a patient treated very promptly after envenomation, before early laboratory abnormalities can occur, although this has not been reported. In general, however, a patient with normal platelet count and absence of FDP elevation during the hospital phase of care is likely not to show coagulopathy at follow-up. A patient with thrombocyto-

Table.
Recommendations for indications for retreatment of recurrent coagulopathy with FabAV.

Fibrinogen <50 μg/mL
Platelet count <25,000/mm^3
INR >3.0
aPTT >50 seconds
Multicomponent coagulopathy
Worsening trend in patient with prior severe coagulopathy
High-risk behavior for trauma
Comorbid conditions that increase hemorrhagic risk

penia or hypofibrinogenemia on presentation or during initial hospitalization should have close follow-up for recurrence, which is generally apparent by the second to fourth day after completion of antivenom treatment. Recurrence is expected to be similar in kind and degree to the original coagulopathy.

Until more data on follow-up are available, we recommend that all FabAV recipients be reevaluated at least once within 5 days after antivenom treatment; if laboratory values remain normal during this time, recurrence is unlikely. Patients at risk for recurrence (those with abnormal coagulation during the first 36 hours) should be reassessed more often—approximately every 48 hours after the last antivenom dose, until coagulation values are clearly stable or improving for several days. If coagulation values become significantly abnormal on follow-up, or if there is a definite downward trend, then laboratory test results should be monitored daily and consideration should be given to retreatment with antivenom (Figure).

There are at present insufficient data to prove conclusively either that recurrent coagulopathy causes a significant risk of hemorrhage or that recurrence can be prevented by scheduled doses of FabAV. Assuming that the cause of recurrent hypofibrinogenemia, thrombocytopenia, or both is rising plasma venom concentrations, it is uncertain how much antivenom may be needed to neutralize the circulating venom. Although all related data indicate the risk of spontaneous hemorrhage is probably very small, extremely low levels of fibrinogen or platelets almost certainly increase the risk of bleeding in the event of trauma or surgery. Until more data are available, we recommend consideration of retreatment with FabAV in the following circumstances: (1) fibrinogen concentration less than 50 μg/mL, platelet count less than 25,000/mm^3, INR greater than 3.0, or aPTT greater than 50 seconds; (2) multicomponent coagulopathy with abnormal laboratory values of a lesser degree; (3) a clear worsening trend at follow-up in patients who had a severe early coagulopathy; or (4) high-risk behavior or comorbid conditions (Table).

Antivenom given at the first signs of recurrent coagulopathy may be more effective than antivenom administered later in the course. Relatively low levels of circulating antivenom seem to be required for initial reversal of coagulopathy. Although there is not yet enough information to make definitive recommendations for prevention or treatment of recurrent coagulopathy, we suggest when treatment is indicated that 2 vials be given and the effect monitored closely. Additional antivenom may be needed. Coagulation parameters should be followed at least daily and patients cautioned to avoid activities at high risk for trauma. Rehospitalization should be considered for significant hemorrhage or for patients at higher risk because of underlying medical conditions.

In summary, recurrent crotaline venom effects after treatment with FabAV are likely a consequence of pharmacokinetic and pharmacodynamic differences between venom and antivenom. To prevent local recurrence, FabAV should be administered in multiple doses for at least 18 hours after envenomation. Additional doses may be needed in patients who experience severe recurrent coagulopathy. The duration of therapy depends on individual risk factors and coagulation response.

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